



SEP 25 2003

The Honorable Mark E. Souder
Chairman
Subcommittee on Criminal Justice,
Drug Policy, and Human Resources
Committee on Government Reform
House of Representatives
Washington, D.C. 20515-6143

Dear Mr. Chairman:

Thank you for the letter of June 26, 2002, regarding the promotion of marijuana for medical use. As you know, marijuana has not been approved for medical use in the United States. Despite its status as an unapproved new drug under the Federal Food, Drug, and Cosmetic (FD&C) Act, there has been considerable interest in its use for the treatment of a number of conditions.

The Department of Health and Human Services (HHS) has been actively involved in evaluating the current state of knowledge regarding the therapeutic use of marijuana. This evaluation indicates that sound scientific studies supporting the claims of marijuana's usefulness as medication are lacking, despite anecdotal claims to the contrary. A review of the existing pre-clinical and human data does not support the safety or efficacy of marijuana for any indication. In fact, as noted in your letter, there is some concern that the use of smoked marijuana may be harmful to individuals suffering from the conditions for which it is touted as a safe and effective treatment.

Accordingly, HHS does not support facilitating the availability of marijuana for medical use until it has been proven safe and effective as required by Federal law. However, as indicated by the enclosed 1999 "Guidance on Procedures for the Provision of Marijuana for Medical Research," controlled multi-patient clinical trials that comply with all applicable Federal statutes and regulations are permitted to study the safety and efficacy of marijuana.

We appreciate your concerns and have restated your questions and provided answers below.

1. Has smoked marijuana been reviewed and approved by the FDA as a safe and effective medicine?

Botanical marijuana has not been approved by the Food and Drug Administration (FDA) as a safe and effective drug.

2. What, if anything, is the FDA doing to stop the illegal promotion and use of marijuana?

As you are aware, marijuana is controlled under Schedule I of the Controlled Substances Act (CSA). Schedule I substances have a high potential for abuse, no accepted medical use in the U.S., and are not safe for use under medical supervision. HHS recently performed a scientific and medical evaluation of marijuana and provided its recommendation to the Drug Enforcement Agency (DEA) that marijuana remain in Schedule I pursuant to section 201(b) of the CSA. HHS's scientific and medical evaluation and scheduling recommendation can be found at Volume 66, *Federal Register*, page 20038 (April 18, 2001). After receiving HHS's evaluation and recommendation, DEA is responsible for scheduling substances and has primary responsibility for the regulation and distribution of Schedule I substances. FDA generally defers to DEA on criminal enforcement efforts related to Schedule I controlled substances. The criminal penalties for distribution of a Schedule I controlled substance are far greater under the CSA than those available under the FD&C Act for the distribution of an unapproved new drug.

3. Is marijuana an exceptional case or are there other drugs that the FDA has allowed to be made available on a state-by-state basis without first undergoing FDA clinical trials and receiving approval as being safe and effective for patient use?

At this time, botanical marijuana is not an FDA approved drug. As you know, the FD&C Act prohibits the sale of unapproved drugs. Clinical trials (trials in humans) are required to demonstrate that a drug is safe and effective and provide the basis for FDA approval of a drug.

State laws known as "medical marijuana" laws are generally amendments to the state's criminal statute that modify state criminal penalties for those that possess marijuana for medical use. These state laws do not change the Federal prohibition on the sale of an unapproved drug or the unauthorized distribution of a Schedule I substance. In fact, in 2001, the U.S. Supreme Court held that there was no medical necessity exception to the CSA prohibitions on the manufacture and distribution of marijuana (*United States v. Oakland Cannabis Buyers' Cooperative*, 532 U.S. 483).

4. Since marijuana is not available from any manufacturers who have received FDA approval to produce the drug, how can the FDA ensure that marijuana being used under the guise as medicine is not contaminated with other harmful ingredients or that the facilities of those currently providing marijuana meet FDA manufacturing safety standards?

HHS ensures that the marijuana that is being used in legitimate medical research is safe for that research. Currently, the National Institute on Drug Abuse (NIDA), a component of the National Institutes of Health, is the sole source for legal marijuana in the U.S., and this supply is only available for authorized research. NIDA oversees the cultivation of research-grade marijuana on behalf of the U.S. government, assuring that the marijuana used for legitimate approved research has a consistent and predictable potency, is free of contamination and is available in sufficient amounts to support the needs of the research. Clinical research with marijuana must be conducted under an investigational new drug application granted by FDA, requires Institutional

Review Board approval, and requires approval and a special Schedule I license issued by DEA. FDA has limited, if any, jurisdiction over the illegal and/or individual cultivation of marijuana for personal use (see HHS Guidance on Procedures for the Provision of Marijuana for Medical Research, dated May 21, 1999).

5. What precedent does the availability of a drug that has not undergone trials or been approved by the FDA set? Will the manufacturers of other illegal drugs or even legitimate health products be permitted to promote and distribute their products without FDA review or approval?

Under the FD&C Act, an application must be submitted to FDA before clinical research (research in humans) is conducted on a new drug, and a new drug must be approved by FDA prior to its marketing and distribution in the U.S. There have been instances whereby new drugs have been illegally distributed and marketed without FDA knowledge. However, once notified, FDA's Office of Compliance and Office of Criminal Investigation have taken appropriate enforcement action, which may include seizures and injunctions as provided by the FD&C Act, and/or obtaining assistance from other government sources, including DEA if the substance at issue is a controlled substance.

Botanical marijuana is not an FDA approved drug. As noted in your letter, two drugs, which contain one of the active ingredients that is present in botanical marijuana (marinol and nabilone), are approved for therapeutic use in the U.S. The FD&C Act and the *Code of Federal Regulations* (CFR) delineate the requirements for studying investigational drugs, the drug review process, and the marketing of new drugs (see section 505 of the FD&C Act and Title 21, CFR, Parts 312 and 314).

6. What penalties, if any, is the FDA levying on those who are prescribing and selling marijuana for "medical" use?

As stated above, FDA generally defers to DEA and the states for matters related to the illegal distribution of controlled substances.

Thank you again for contacting us concerning this matter. If you have further questions, please let us know.

Sincerely,



Amit K. Sachdev
Associate Commissioner
for Legislation

Enclosure

cc: The Honorable Elijah E. Cummings
Ranking Member
Subcommittee on Criminal Justice,
Drug Policy, and Human Resources
Committee on Government Reform
House of Representatives
Washington, D.C. 20515-2007

ANNOUNCEMENT OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES' GUIDANCE ON PROCEDURES FOR THE PROVISION OF MARIJUANA FOR MEDICAL RESEARCH

Release Date: May 21, 1999

National Institutes of Health

I. Introduction

The intent of this document is to provide guidance to the biomedical research community who intend to study marijuana in scientifically valid investigations and well-controlled clinical trials on the procedures of the Department of Health and Human Services (HHS) for providing research-grade marijuana to sponsors. (i)

The production and distribution of marijuana for clinical research, is carefully restricted under a number of federal laws and international commitments. The manufacture, acquisition, and distribution of marijuana is subject to control under Schedule I of the Controlled Substances Act (CSA) (21 U.S.C. 801 et seq.), the most restrictive of the five federally regulated classes of controlled substances. Persons who wish to conduct research using Schedule I substances such as marijuana must obtain a special registration under the CSA from the Drug Enforcement Administration (21 U.S.C. 823(f)). To receive such a registration, a researcher must first be determined by HHS to be qualified and competent, and the proposed research must be determined by HHS to have merit (id.). Moreover, persons who intend to study marijuana for use in the cure, mitigation, treatment, or prevention of disease are subject to the "drug" and "new drug" provisions of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321 et seq.).

The United States is also a party to the Single Convention on Narcotic Drugs, an international narcotics control treaty. Parties to the Single Convention have agreed to limit production, distribution, and possession of cannabis and cannabis resins to authorized medical and scientific purposes (Art. 4). In addition to these and other controls, Articles 23 and 28 of the Single Convention provide that if a country allows cultivation of the cannabis plant for research purposes, the country must establish a national agency to control the cultivation and distribution of the crop. Currently, the National Institute on Drug Abuse (NIDA), a component of the National Institutes of Health (NIH), oversees the cultivation of research-grade marijuana on behalf of the United States government.

An appropriate scientific study of a drug substance requires, among other things, that the substance used in the research must have a consistent and predictable potency, must be free of contamination, and must be available in sufficient amounts to support the needs of the study. NIDA allocates resources to cultivate a grade of marijuana that is suitable for research purposes. Recently, there has been considerable interest in determining, through scientifically valid investigations, whether cannabinoids can provide positive medical benefits. In February 1997, an NIH-sponsored workshop analyzed available scientific information and concluded that "in order to evaluate various hypotheses concerning the potential utility of marijuana in various therapeutic areas, more and better studies would be needed." (ii) Most recently, the Institute of Medicine issued a detailed report that supports the absolute need for evidence-based research into the effects of using marijuana and, in particular, the cannabinoid components of marijuana, for patients with specific disease conditions. (iii) Moreover, recent State-level public initiatives, including referenda in support of the medical use of marijuana, have generated additional interest in the medical community for high quality clinical investigation and comprehensive safety and

effectiveness data.

Against this backdrop are the real concerns regarding the toxicity of smoked marijuana. Indeed, the IOM report emphasized that smoked marijuana is a crude drug delivery system that exposes patients to a significant number of harmful substances and that "if there is any future for marijuana as a medicine, it lies in its isolated components, the cannabinoids and their synthetic derivatives". As such, the IOM recommended that clinical trials should be conducted with the goal of developing safe delivery systems.

HHS recognizes the need for objective evaluations of the potential merits of cannabinoids for medical uses. If a positive benefit is found, HHS also recognizes the need to stimulate development of alternative, safer dosage forms. Through this document, HHS is announcing procedures that are intended to facilitate the research needed to evaluate these pending public health questions by making research-grade marijuana available for well-designed studies on a cost-reimbursable basis.

II. Availability of Marijuana for Research Purposes

To facilitate research on the potential medical uses of cannabinoids, HHS has determined that it will make research-grade marijuana available on a cost-reimbursable basis, subject to the priorities and conditions described in section III, below.

HHS will also consider the extent to which a proposed study incorporates the trial design elements outlined by the participants in the 1997 NIH Workshop. Such studies are the most likely to yield high quality, scientifically valid data on the safety and effectiveness of cannabinoids. The goal of this program must be to determine whether cannabinoid components of marijuana administered through an alternative delivery system can meet the standards enumerated under the Federal Food, Drug, and Cosmetic Act for commercial marketing of a medical product (see e.g., 21 U.S.C. 355). As the IOM report stated, "Therefore, the purpose of clinical trials of smoked marijuana would not be to develop marijuana as a licensed drug, but such trials could be a first step towards the development of rapid-onset, nonsmoked cannabinoid delivery systems."

III. Elements for Considering Proposed Studies

The focus of HHS's program is the support of quality research for the development of clinically meaningful data. HHS intends to make available a sufficient amount of research-grade marijuana to support those studies that are the most likely to yield usable, essential data. However, it should be noted that NIDA's supply of marijuana is subject to a number of constraints associated with the cultivation of a research-grade crop and that the supply at times may be variable.

For protocols submitted by non-NIH funded sources, institutional peer-review is strongly recommended prior to submission to HHS. After submission, the scientific merits of each protocol will be evaluated through a Public Health Service interdisciplinary review process. This process will take into consideration a number of factors, including the scientific quality of the proposed study, the quality of the organization's peer-review process, and the objectives of the proposed research. For example:

The extent to which the protocol incorporates the elements of good clinical and laboratory research;

The extent to which the protocol describes an adequate and well-controlled

clinical study to evaluate the safety and effectiveness of marijuana and its constituent cannabinoids in the treatment of a serious or life threatening condition;

The extent to which the protocol describes an adequate and well-controlled clinical study to evaluate the safety and effectiveness of marijuana and its constituent cannabinoids for a use for which there are no alternative therapies;

The extent to which the protocol describes a biopharmaceutical study designed to support the development of a dosage form alternative to smoking;

The extent to which the protocol describes high-quality research designed to address basic, unanswered scientific questions about the effects of marijuana and its constituent cannabinoids or about the safety or toxicity of smoked marijuana.

In the event that supplies become limited, marijuana will be made available in the order of priority described below.

1. Protocols that have been reviewed and funded by NIH.
2. Protocols sponsored or conducted by other governmental organizations.
3. Protocols sponsored or conducted by other sources.

The sponsor of a proposed protocol must be able to demonstrate the ability to fully reimburse NIDA's contractor for the cost of research-grade marijuana supplied through the completion of the study. In addition, researchers who propose to conduct investigations in humans must be able to fulfill the Food and Drug Administration's investigational new drug (IND) requirements and must obtain a valid registration from the Drug Enforcement Administration (DEA) for research with Schedule I drugs.

IV. Marijuana Trial Design Elements

A clinical study involving marijuana should include certain core elements, many of which reflect recommendations made by the 1997 NIH Workshop. A study that incorporates the NIH Workshop recommendations will be expected to yield useful data and therefore, will be more likely to be eligible to receive marijuana under the HHS program. The full report can be accessed on the Internet at <http://www.nih.gov/news/medmarijuana/MedicalMarijuana.htm>. HHS will consider if additional guidelines are needed on the essential elements of clinical trial design for medical marijuana studies.

HHS also notes that within each of the categories described in section III, preference will be given to those protocols that are designed around specific safety or efficacy endpoints. Protocols for open-ended or "ongoing" trials that do not include ending dates are not likely to be eligible to receive marijuana. In addition, proposed protocols must be determined to be acceptable under FDA's standards for authorizing the clinical study of investigational new drugs, which state in part:

FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety. Therefore, although FDA's review of Phase 1 submissions will focus on assessing the safety of Phase 1 investigations, FDA's review of Phases 2 and 3 submissions will also include an assessment of the scientific quality of

the clinical investigations and the likelihood that the investigations will yield data capable of meeting statutory standards for marketing approval.

21 CFR 312.22(a).

Finally, HHS intends to direct its program toward multi-patient clinical studies. As previously determined by the Public Health Service, single-patient requests for marijuana raised a number of concerns including the fact that the single-patient IND process would not produce useful scientific information and we do not foresee that they would be supported under this program.

V. Procedures for Obtaining Research-Grade Marijuana

Researchers who intend to conduct clinical studies of marijuana should first make an inquiry to NIDA to determine the availability and costs of marijuana. Such an inquiry must address the considerations outlined in sections III and IV of this document for establishing research priority.

Because research-grade marijuana will be provided to researchers on a cost-reimbursable basis only, researchers also will be expected to include a plan for ensuring timely reimbursement for all costs associated with the cultivation and delivery of the marijuana.

In addition, specific information (including full justification) should be provided as to the number and potency of marijuana cigarettes or bulk marijuana needed, and the timing of the intended use of the marijuana. This information must be updated annually with NIDA in order that adequate supplies can be maintained and future needs estimated. Continued provision of marijuana is subject to availability and to continued compliance with these policies and procedures and with all applicable statutes and regulations.

This information and requests to NIDA concerning availability and costs should be sent to:

Program Administrator
Drug Supply and Analytical Services
National Institute on Drug Abuse
6001 Executive Blvd
Bethesda, MD 20892

If NIDA determines that marijuana is available to support the study, NIDA will provide the researcher with authorization to reference NIDA's marijuana Drug Master File (DMF).

If the researcher is proposing a study in humans, after obtaining the right of reference to the DMF, the researcher must proceed through the FDA process for filing an IND application under 21 CFR part 312. Information on the requirements for obtaining an IND can be found on the FDA web site at <http://www.fda.gov>.

In addition, all researchers must obtain from DEA registration to conduct research using a Schedule I controlled substance. Information on the requirements for obtaining a DEA registration for research with marijuana can be obtained following the process outlined in 21 CFR part 1301.

VI. Implementation

This procedure will apply to the provision, through NIDA, of marijuana

cigarettes (of varying THC content, including placebo), as well as bulk marijuana. HHS will apply this procedure beginning on December 1, 1999. HHS will re-evaluate these procedures periodically and determine within five years whether or not the procedures should be continued. Requests for marijuana may be submitted prior to that time. However, shipments should not be expected before then and definitive information regarding costs may not be available until that time.

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- i Once implemented, this document will represent HHS's current approach with respect to biomedical research involving marijuana. It does not create or confer any rights for or on any person and does not operate to bind HHS or the public. An alternative approach may be used if such an approach would satisfy all applicable legal requirements.
 - ii Workshop on the Medical Utility of Marijuana: Report to the Director, National Institutes of Health. National Institutes of Health, February 19-21, 1997.
 - iii "Marijuana and Medicine: Assessing the Science Base", Institute of Medicine, March 17, 1999.

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